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FDA REGULATION OF HOME-USE IN VITRO DIAGNOSTIC DEVICES

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The Food and Drug Administration's Regulatory Paradigm for In Vitro Diagnostic Devices

In 1976 Congress passed the Medical Device Amendments' to the Food, Drug, and Cosmetic Act, initiating oversight of medical devices by the Food and Drug Administration (FDA). Since the definition of devices included any device " intended for use in the diagnosis of disease or other conditions" [1], in vitro diagnostic devices (IVDs) were included under this new regulation. This law established several requirements including the need for IVD manufacturers to register with the FDA and list their products, to comply with good manufacturing practices, and to report serious device failures. This provided the Agency with a listing of tests in the marketplace, mechanisms to assure that medical devices were made using sound manufacturing practices, and a system to identify serious problems related to device failure, so that FDA could interact with companies in identifying mechanisms for dealing with these problems. In addition to these general controls, the new law also put into place requirements for premarket review of medical devices entering the market for the first time.

Two types of premarket submissions were established. Devices similar to existing marketed devices are "cleared" as premarket notifications if they demonstrated substantial equivalence to the previous device. Because the portion of the law describing this is the 5 10(k) section, these are referred to as 510(k) submissions. Fundamentally new devices are "approved" as premarket approval applications. These are referred to as PMAs.

In the semantic framework of FDA language, a determination of whether a device is considered old or new is based on identification of a predicate – a device that was

legally marketed prior to May 28, 1976 or a device which has been found substantially equivalent by FDA to such a previously marketed device – against which the device can be compared. An in vitro diagnostic test is essentially a laboratory test.

Premarket Notifications

Most IVD submissions are premarket notification or 5 1 O(k) s. The agency currently handles approximately 1000 of these per year. The operative term in 5 1 O(k) review is "substantial equivalence." The law requires, as noted above, that new versions of existing devices be substantially equivalent to a predicate device. Review of most 5 1 O(k) submissions is straightforward and based on an analysis of the fundamental performance of a test including accuracy, precision, analytical sensitivity, and analytical specificity. There are limitations to the review process. 5 1 O(k) review is entirely a paper review; FDA does not submit these products to direct laboratory evaluation and the agency therefore has no hands-on experience with the vast majority of devices it considers. In addition, the agency is continually challenged by the need to determine appropriate standards for the substantial equivalence decision, since these are not well addressed in either the laboratory medicine or clinical literature. The 5 1 O(k) review process has well established administrative requirements and a targeted FDA review time of 90 days. Inform&ion on this type of submission can be obtained on the FDA home page (www.fda.cdrh.gov) or by calling the Division of Small Manufacturers Assistance (l-800-638-2041).

Premarket Approval Applications

The agency reviews far fewer IVD premarket approval submissions - generally 1

to 2 dozen are under review in the course of a year. The key factor in a PMA review is "safety and effectiveness." Since no predicate can be defined, it is necessary to establish independently that the product is "safe and effective." In fact, since passage of the Safe Medical and Devices Act of 1990[2], FDA has taken a broader interest in the safety and effectiveness of all devices. We now require for 5 1 O(k) submissions either a summary of safety and effectiveness or a statement that the company will make available all information in the premarket submission on safety and effectiveness upon request.

For all PMAs and for at least a subset of 5 1 O(k)s FDA now has data requirements which include not only the analytical performance of a device but clinical performance as well, including clinical or diagnostic sensitivity, clinical or diagnostic specificity, and in some cases information on the expected predictive values of testing. Limitations of the review are again obvious. In evaluating new products there is often a lack of a "gold standard" against which to judge performance. Bias may occur in collection of data to establish safety and effectiveness through problems in the study design or conduct. Finally, as with 5 1 O(k) submissions, determining the minimum performance required for approval can be difficult and challenging. The PMA review process, like the 5 1 O(k) process, has well-established administrative requirements. Because these submissions are often more complex than 5 1 O(k)s the targeted FDA review time is 1 SO days. Information on this type of submission can also be obtained on the FDA home page (www.fda.cdrh.gov) or by calling the Division of Small Manufacturers Assistance (l-800-638-2041).

Labeling of In Vitro Devices

In vitro devices are unique in that they have there own labeling regulations – CFR

809.10. These regulations clearly specify the information required to support device labeling and submissions. The labeling regulation is divided into 15 separate components, which are outlined in Table 1.

Of these various elements the most important is evaluation of the intended use and the related indications for use. The intended use and indications for use of a product will determine the type of review (whether a product is a 5 10(k) or PMA), the questions likely to be raised, and the data likely to be required in the course of review.

Development of a Standardized Scientific Review Model

A central concern of FDA over the past several years has been development of a strong but pragmatic scientific model to frame our review. The agency believes that while there is not one path to truth in terms of the development of information to support product review, there are several basic tenets for good science. These include the need for

* Up-front design of the study. All submissions whether simple or complex require an established design in advance of the study. In some cases all that is needed is referencing the NCCLS or other voluntary evaluation standards that will be used; in others there may be a need to develop extensive and complex protocols with carefully formulated hypotheses. Design of the study in advance helps prevent bias and assures that the data obtained will address the intended use and advertising claims desired.

* Careful and meticulous collection of data. Careful execution of the study following the protocol is essential to obtain useful data. Each step of testing should be carefully conducted and documented so that any questions regarding the results can be answered later.

* Interpretation of results using sound, preferably referenceable, statistical techniques.

A statistical plan for analyzing results should be prepared in advance of testing and included in the protocol. Results must be analyzed according to this plan.

Individual product review obviously varies by the type of product and intended use.

Review of Quantitative Tests

For a quantitative test, 5 1 O(k) review focuses on information on bias or, if possible accuracy, comparing the new method, by linear regression or other valid statistical techniques to a reference and/or a predicate method; information on precision, ideally studied using an ANOVA analysis to allow comprehensive assessment of components of variation; and experiments designed to evaluate analytical specificity and, if appropriate, sensitivity.

Review of Qualitative Tests

For a qualitative test, 5 1 O(k) review requirements usually require all of the information requested for quantitative tests but in addition seek information on cut-off points established and discrimination or equivocal zones present in the test system.

For certain submissions, clinical as well as analytical data is required, to allow test performance to be analyzed within a clinical framework. FDA prefers when possible that information on clinical performance characteristics be defined in terms of receiver operator characteristic (ROC)) curves.

The Scope of Food and Drug Administration Review Requirements

FDA review has historically not required outcome data showing how new tests will impact morbidity or mortality and/or actually change the quality of medical care. The presumption that clinical information is useful usually suffices to support the review

process and FDA works closely with sponsors of new tests to help them identify appropriate clinical or laboratory end-points or surrogate end-points on which to establish test performance and to base test claims. In some instances a new test may have no obvious potential clinical use and no clear measure of effectiveness. In these cases medical literature and/or clinical outcome data may be required to demonstrate safety and effectiveness. FDA review for IVDs generally does not require the type of prospective clinical studies often needed for more invasive devices. Prospective studies are required in only a handful of new tests, most commonly those in which the clinical claim involves a prediction of future endpoints or outcomes. Usually concurrent sample analysis comparing new tests to one or more predicate tests or reference methods can be used to support product review and timely clearance or approval.

FDA review does require meticulous attention to detail in data collection and presentation. A sponsor by providing a high quality study and a clear and well written submission makes the agency's review job simpler and helps assure success for the company in bringing the product to market quickly.

Premarket review by FDA is conducted for the purpose of assuring the safety and effectiveness of in vitro diagnostic products. FDA contributes to quality of marketed IVD's in at least three ways: it provides for oversight and objective review of new laboratory tests, sets minimum thresholds for product safety and effectiveness, and finally, ensures that organized data and appropriate labeling is provided to the users in support of a device's intended use.

The Regulation of Home-Use In-Vitro Diagnostic Devices

Home use tests have been commercially marketed in the United States for more

than twenty-five years. At the time of passage of the Medical Device Amendments in 1976 at least two important products were being sold over the counter. The first was the urine dipstick for evaluation of glucose and other common analytes. The second was the urine pregnancy test.

Following the passage of the Medical Devices Amendments, the first home use test, was cleared by FDA in 1979 (a urine glucose test). Since then the agency has reviewed and cleared more than 300 in vitro diagnostic tests for home use in twelve diagnostic categories (Table 2). Twenty-seven were cleared in 1997 alone. A comprehensive list of products cleared for home use can be found on the FDA inter-net (www.fda.gov/cdrh/ode/otclist.html).

FDA's approach toward regulation of this type of product was first outlined in 1988 with the publication of a guidance document entitled "Assessing the Safety and Effectiveness of Home-Use In Vitro Diagnostic Devices (IVDs): Draft Points to Consider Regarding Labeling and Premarket Submissions[3]." This document which was created with input from representatives of industry and professional groups as well as consumers is designed to assist manufacturers of home-use in vitro diagnostic devices comply with existing regulations and premarket clearance requirements. The document outlines the key parameters of importance in the FDA review of home-use devices:

* The test when used in the hands of the lay user should produce acceptable results when compared to results performed in the hands of professional users.

* Test results should be interpretable by lay users

* The benefits of use should be found to outweigh the risks.

Evaluation of Home-Use Performance in the Hands of Lay Users

Documentation of the first point is usually based on field studies designed to mimic real world use. Data sets from lay users are used to establish key performance parameters such as accuracy and precision in the hands of these untrained users. FDA suggests that these studies be done in a population representative of the population likely to purchase the device. Optimally populations studied should include a broad base so that performance is assessed with in individuals from a wide variety of socioeconomic, educational, and cultural backgrounds.

FDA also suggests that the studies replicate as closely as possible the likely real world use. Tests are often used by consumers at home without oversight, following their normal daily schedules. Instructions for use in a study normally are the sarne as would be expected in the final labeling. Special training programs or materials may be used as part of a study only if the intention is to make these same materials available during the actual use of the product. FDA also encourages manufacturers to perform both observational studies of consumers using the product and focus testing with small groups of users to ensure that performance is adequately characterized, design features are understood, and labeling is optimized for correct use.

Evaluation of Home-Use Benefits and Risks in the Hands of Home Users

The second point and third points require a clinical evaluation of the test and an intense review of proposed labeling. FDA's review of the merit of a home test takes into account the impact of home access to test results, A major issue in this evaluation is whether information can be clearly communicated to lay users and would be expected to lead to actions that promote personal or public health and minimize illness.

At least two questions are posed during FDA review regarding benefits of the

device, both outlined in the 1988 home-use document. The first question is focused on the clinical benefit of the test to the patient in terms of screening, diagnosing, or monitoring a particular disease, condition, or risk factor. The second is focused on the benefits to the patient of having the test available for home-use as opposed to having the test performed by health care professionals.

At least two questions are also posed regarding risks of the device during FDA review. The first is what is the impact on the user of a false-positive or false-negative result? The second is what are the risks to the user in terms of delay in obtaining a professional examination if a proposed home-use IVD that is intended for use on symptomatic subjects gives a false or equivocal result?

Requirements for Home-Use Performance

In the 1988 guidance document FDA outlines three considerations in evaluating the performance of a home-use device. First the home-use IVD should perform as well as the professional-use equivalent. Second the home-use device should be designed with a view to ensuring that the device's performance will not be appreciably affected by expected variation in user technique or environment. Finally, the home-use device should include a simple method by which consumers can determine if the test is working properly. Most frequently this involves providing either a user quality control system in the kit or a "built in" form of quality control.

Requirements for Home-Use labeling

Because of the wide variation expected in education and competency of the home-use operator, FDA has developed extensive recommendations, which can be followed by manufacturers to develop user-friendly labeling[3]. In addition, the agency frequently cites

an NCCLS document [4] with advice on home labeling. This document includes information on techniques for evaluating the reading level of a label -- FDA requires these products to be targeted at an 8th grade reading level. The document also includes information on how test reliability can be reported in a manner understandable by lay users. Finally, the agency encourages use of a monograph published by FDA in 1993 entitled "Write it Right" which provides manufacturers with further instructions on the development of user friendly language for lay consumers'.

Basic points checked in labeling review are: the need for simplicity and brevity, the use of diagrams and pictures to reinforce text, providing information in a question and answer format, and the identification of a technical assistance number to provide technical support and advice to individuals using a test.

The Status of Home-Use Tests

As noted above although a large total number of individual devices have been cleared for home use, these represent a relatively small number of test types (Table 2). Until the end of 1996, only the first seven categories had been approved for marketing

Marketing of urine cups for collecting and sending in samples for drugs-of-abuse testing is the result of a special initiative developed by the agency in 1997 to reduce barriers to testing for concerned parents (www.fda.gov/ohrms/dockets/98fr/030598b.pdf). This initiative, which is currently being developed as a final rule,' allows test collection systems to be sold for home-use as long as the sample is sent to a SAMHSA certified laboratory or equivalent, is tested using an FDA cleared or approved product or one recognized as equivalent, and is labeled and processed in a manner to minimize mishandling and generation of incorrect results.

Marketing of filter paper strips for home HIV testing was approved by the Center for Biologics Evaluation and Research after extensive review, public and panel discussion, and determination by FDA that the product produced results equivalent to professional use results and that the public health benefits of increased access to information on HIV status outweighed potential risks. Review of this product involved evaluation of test performance, labeling, and the system used and information provided as a part of call-in test access.

Introduction of New Classes of Home-Use Tests -- Fructosamine and Prothrombin Times

In 1997, FDA cleared two new first-of- a kind tests for use at home. The first was a test for fructosamine. This product was cleared after extensive review of analytical and clinical data and a formal panel meeting to evaluate issues of performance, labeling, quality control, and potential use. The sponsor provided clinical studies and peer-reviewed scientific literature to help establish user-friendly cut-off points to maximize the chance for proper interpretation by lay users. The fructosamine was an unusual choice for a home use test because in spite of a large body of literature supporting its use, it is not commonly requested by health care professionals. This test was viewed as a low risk addition to those currently in use for monitoring glucose control.

The second type cleared were two tests for home measurement of prothrombin times (PT). These products were also cleared after extensive review of analytical and clinical data, after a panel meeting to discuss the relevant review issues, and with agreements by the involved sponsors to undertake postmarket studies to assess the real world performance of these devices over time.

Clearance of the prothrombin time tests was a milestone for FDA. We believed that these devices afforded the potential for unique benefits. Clinical experience in Europe with home PT testing has clearly demonstrated improved anticoagulant status and patient outcomes. We also believed that these devices afforded the potential for unique risks in terms of testing or dosing errors.

As a result of this unique set of benefits and risks, our review division suggested, the hematology panel supported, and the device sponsors accepted the use of a special designation for this test category. These devices were cleared for "home use by prescription" rather than direct sale over the counter. The designation prescription home use devices is one that has been used on occasions in the past for other medical devices. However, these two new prothrombin time tests represent the first application of this restriction for in vitro diagnostic products. The obvious significance in this designation is the requirement that a physician be involved in choosing patients, who are appropriate candidates for home testing, be responsible for appropriate training of the patient and for oversight of the home testing system, and be involved in doing dosage changes, which might occur as a result of home test results.

FDA review of these products focused not only on the issues of performance and use but also on the specific user training programs developed by each of the device sponsors.

Introduction of a Home-Use Screening Test for Drugs of Abuse

In 1998 the home-use market yet again expanded with clearance of the first home drug-screening test for drugs of abuse. This product was also the result of extensive policy and submission guidance development, deliberation by a formal panel meeting to

discuss scientific and regulatory issues, and a careful review of risks, benefits, and requisite labeling. Clearance of this product as a 510(k) was based on establishing a framework to maximize benefit and minimize risk of this device. The device is configured to read out results only as inconclusive (requires further testing) or negative. The cost of confirmatory testing for inconclusive results is expected to be built into the cost of the product. Home-use testing results demonstrated the ability of this test to produce negative and inconclusive results with the same performance as that expected for a comparable point-of-care test.

The Future of Home-Use Testing

FDA expects continued growth in the number and scope of products offered for home-use. Interest in this market is made possible by improved technologies, which allow products to be designed for reliable use in the home setting. The increased health consciousness of the general public, changes in the health care system with a focus on preventive care and cost containment, and the need for increased and easier access to health information, including the results of laboratory testing, all will continue to encourage expansion of this new part of the IVD market.

Although the agency is currently initiating a number of reengineering initiatives based on decreasing resources, and a number of review reforms are occurring in response to the new FDA Modernization Act of 1997[6], the agency continues to view near-patient testing and home-use testing in particular as devices which deserve continued close regulatory oversight.

References:

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2. Safe Medical Devices Act of 1990. Pub L. No 101-629, 104 Stat 4523

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4. NCCLS. *Labeling of HomeUse In Vitro Testing Products: Approved Guideline.* NCCLS document GP14-A (ISBN 1056238-299-3). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 10897, 1996.

5. Backinger CL and Kingsley PA. *Write It Right.* U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Devices and Radiological Health, 1993.

6. FDA Modernization Act. Pub L. No. 105-l 15, 133 Stat 830.

TABLE 1: FDA Labeling Requirements

- The proprietary name and established name
- Intended Use
- Summary and explanation of the test
- The principle of the procedure.
- Information on reagents
- Information on instruments (operation manual)
- Information on specimen collection and preparation
- Procedures
- Results
- Limitations of the procedures
- Expected values
- Specific performance characteristics
- Bibliography
- Name and place of business
- Date of the last revision of the package insert

Table 2: Categories of IVDs Cleared by FDA for Home-Use

- Glucose
- Cholesterol
- Fecal occult blood
- Human chorionic gonadotropin
- Luteinizing hormone
- Urine dipsticks
- Filter paper collection strips for glycohemoglobin
- Filter paper collection strips for antibody to HIV
- Collection devices for drugs of abuse
- Fructosamine
- Prothrombin Time
- Point of care drugs of abuse